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MEN, WOMEN AND PRIMARY LUNG CANCER—A SASKATCHEWAN PERSONAL INTERVIEW STUDY

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Abstract—In a previous study conducted by mail questionnaire and with a large proportion of surrogate responders, we found differences in smoking habits, age at diagnosis, tumour cell type distribution and occupational exposures between men and women who developed primary lung cancer. This study was designed to confirm those findings by conducting personal case interviews and extend them by examining the impact of certain biological factors. We have investigated demographic, smoking, occupational and medical history sex differences in cases with primary lung cancer by interviewing 273 male and 103 female cases diagnosed between November 1983 and July 1986. The females were significantly younger at diagnosis, a pattern consistent for all cell types. Squamous cell (40%), small cell anaplastic (20%) and adenocarcinomas (16%) were the most prevalent cell types in men. In women, similar frequencies of adenocarcinomas (32%) and squamous cell carcinomas (29%) occurred. Despite a higher prevalence of physician diagnosed allergy and asthma among women, minimal sex differences in the prevalence of atopy as measured by prick skin test were found. Female cases were more likely to be lifetime non-smokers (15% vs 3%), to have started smoking on average 3 years older and to smoke 6 fewer cigarettes per day. The mean pack years of female cases was significantly lower than males' for squamous, adenocarcinoma and small cell anaplastic tumours. The majority of these women had not been occupationally exposed to any substance known to be carcinogenic or to damage the lung. However, in a small subset of cases pulmonary function variables were as depressed in women as in men with significantly higher mean pack years. Our results do not appear to be due to a cohort effect as all trends remain the same when the data were stratified by age at diagnosis. In summary, female cases were diagnosed younger; smoked less, both in terms of duration and dose; and experienced similar levels of pulmonary dysfunction at a lower dose of smoking in comparisons with men. Other factors, for example, occupational exposures and emphysema, which have been shown to increase the risk of lung cancer among males, were less prevalent in female cases.

Primary lung cancer Male/female Pulmonary function

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INTRODUCTION

We have extended previous investigations of sex-dependent differences in characteristics of cases with primary lung cancer [1–11]. In

Saskatchewan, a low incidence area for primary lung cancer, we previously used the records of the Saskatchewan Cancer Foundation and a mailed questionnaire to demonstrate that women with lung cancer were younger than men at diagnosis for each cell type despite the following: (a) more lifetime non-smokers among them; (b) among current and ex-smokers, female's duration of smoking was shorter and their pack years lower; (c) few occupational exposures to act in synergism with cigarette smoking; and (d) minimal differences in the frequency of a positive family history of lung cancer or malignancy at any site between male and female cases [1]. In the present study, we confirm and extend the above results using personal interviews, pulmonary function tests and allergy skin prick tests to investigate more detailed occupational, smoking related and familial health variables.

METHODS

With the cooperation of the Saskatchewan Cancer Foundation, which operates a population-based tumour registry and provincial treatment centres, each newly diagnosed case with primary lung cancer was approached either in person and/or by letter of informed consent to participate in the study. Each case was requested to grant an interview. Selected cases as outlined below were requested to perform pulmonary function tests and be allergy skin tested. The personal interview included in-depth questions concerning occupational exposures, previous personal health, smoking habits and the health of all first degree relatives. The questionnaire is available upon request. This study has the approval of the University of Saskatchewan's President's Advisory Committee on Ethics in Human Experimentation.

Pulmonary function tests were requested only of those cases with non-obstructing coin lesions (<2.5 cm) who had not received any surgical, radiological or chemotherapeutic treatment. One of us (J.A.D.) reviewed the chest X-rays of each case to determine size and location of the tumour. After an instructional session, subjects performed forced expired manoeuvres from total lung capacity to residual volume to obtain the measurements of forced vital capacity (FVC), forced expired volume in 1 sec (FEV_1), $FEV_1/FVC \times 100$ and the maximum mid-expiratory flow rate (MMFR). A Godart Expirograph water spirometer was used. Each subject performed a maximum of six forced expired manoeuvres with the objective of obtaining three consistent spirograms with FVC within 5% of the maximum FVC and FEV_1, within 5% of the best FEV_1. In order to obtain the percentage of predicted values using modified Morris [12] regression equations and a Hewlett–Packard 9826 computer program, the best FEV_1, the best FVC and MMFR from the spirogram with the best FEV_1 were used.

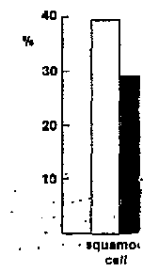
Only those cases who had not received any treatment for their malignancy were eligible for skin testing with seven common allergens and a diluent control (Hollister-Stier Division of Miles Labs Ltd, Rexdale, Ontario). The allergens used were house dust mite (1:100 wt:vol), mixed grain dust (1:10), mixed animal dander (cat 1:30, dog 1:30, horse 1:30), mixed moulds (*Alternaria* 1:60, *Aspergillus* 1:60, *Hormodendrum* 1:60), mixed weed pollen (1:20), mixed tree pollen (1:20) and mixed grass pollen (1:20). The wheal diameters were measured in two perpendicular directions at 10 min and the mean wheal diameter determined as the mean of the measurements.

Additional information concerning the location of the tumour within the lung, the tumour histology and age at diagnosis, was extracted from the records of the Saskatchewan Cancer Foundation. All cases with a diagnosis of primary lung cancer registered between November 1983 and 31 July 1986, and alive 1 month after diagnosis were eligible for the study. A diagnosis based solely on clinical grounds was acceptable if there was convincing radiologic evidence consistent with the symptoms.

Statistical analysis included chi-square for frequency distribution and analysis of variance for quantitative variation.

RESULTS

There were 827 cases diagnosed, 603 men and 224 women, male/female ratio 2.69; 25% of these was deceased within 1 month of the date of registration and were considered ineligible for interview due to ill health; approx. 61% of those eligible was interviewed. The non-interviewed group was older ($\bar{X} \pm SE$, 68.5 ± 0.53 vs 64.3 ± 0.47) and the male/female ratio was slightly higher, 2.76. No significant differences in the distribution of cell type between interviewed and non-interviewed eligible cases were found. An additional 81 subjects returned postal questionnaires. Women were



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Frequent chest colds	
Pneumonia	
Allergies***	
Shortness of bre	
Bronchitis**	
Asthma*	
Emphysema**	
Pleurisy	
TB	
Chest injury***	
Sinus trouble	
Hay fever	
Cancer (other site)	
Heart disease	
Arthritis	

[a]Percentage base
*$p < 0.05$; **$p <$

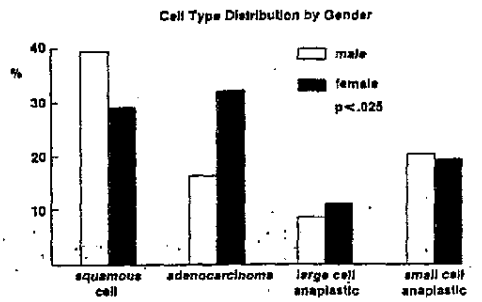

Fig. 1. Histological cell type distribution of interviewed patients stratified by gender (men, $n = 273$; women, $n = 103$). There were 19 individuals designated as clinical, 18 were men.

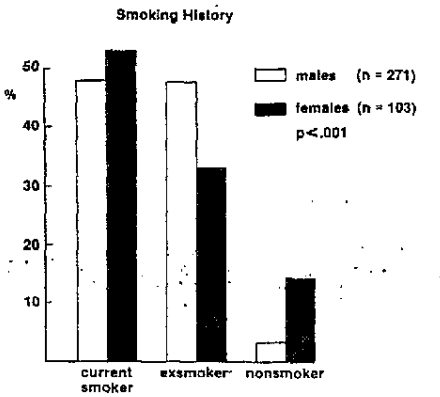

Fig. 2. Smoking history of patients with lung cancer stratified by gender.

younger at diagnosis than men in the entire case population, the eligible subset and the interviewed group.

Interviews were conducted with 376 cases during the specified time period, 273 males and 103 females, male/female ratio = 2.65. Females were younger ($\bar{X} \pm SE$, 60.8 ± 1.0 years) than males (65.7 ± 0.5 years, $p < 0.001$) at diagnosis. This pattern was consistent for all cell types. A preponderance of tumours was located on the right side of the lung (females 54.4%, males 54.9%). The histological cell type distribution was significantly different (Fig. 1). Females had similar percentages of adenocarcinomas (32.0%) and squamous cell tumours (29.1%), while the predominant cell type in men was squamous (39.6%) with only 16.5% classified as adenocarcinomas and 20.1% as small cell anaplastic. 19 interviewed individuals were diagnosed on clinical grounds, 18 were male.

Table 1. Frequency of symptoms and physician diagnosed medical conditions by sex

	Males		Females	
	n	%[a]	*n*	%[a]
Morning cough**	148	54.2	43	41.7
Phlegm**	112	41.0	30	29.1
Wheeze (without cold)	101	37.0	44	42.7
Frequent chest colds	34	12.4	16	15.5
Pneumonia	122	44.7	52	50.5
Allergies***	54	19.8	38	36.9
Shortness of breath	96	35.2	41	39.8
Bronchitis**	69	25.3	39	37.9
Asthma*	17	6.2	13	12.6
Emphysema**	42	15.4	5	4.8
Pleurisy	37	13.6	21	20.4
TB	5	1.8	4	3.9
Chest injury***	75	27.5	9	8.6
Sinus trouble	64	23.4	34	33.0
Hay fever	14	5.1	7	6.8
Cancer (other site)	28	10.3	12	11.6
Heart disease	51	18.7	13	12.6
Arthritis	71	26.0	26	25.2

[a]Percentage based on number responding to each question.
*$p < 0.05$; **$p < 0.025$; ***$p < 0.005$.

Antecedent symptoms and medical conditions

Among the five chronic symptoms tabulated—morning cough, morning phlegm, wheezing, shortness of breath and frequent chest colds—males reported morning cough ($p < 0.025$) and morning phlegm ($p < 0.025$) significantly more frequently than females (Table 1). In response to the question "Has a doctor ever told you that you have ————?", more females reported a history of bronchitis ($p < 0.025$), allergies ($p < 0.005$) and asthma ($p < 0.05$). Males, however, reported chest injuries ($p < 0.005$) and emphysema ($p < 0.025$) more frequently. Minimal differences in the reported frequencies of pneumonia, pleurisy, heart disease or cancer at other sites were found.

A total of 211 males were allergy prick skin tested. Of these, 85 (40.3%) had at least a "one plus" reaction to at least one allergen and 65 (30.8%) scored at least "two plus". Of the 82 females tested, 33 (40.2%) had at least a "one plus" reaction to at least one allergen and 26 (31.7%) scored at least "two plus".

The distribution of malignant disease in first degree family members of male and female cases was similar: at least one relative with (a) lung cancer (16%), (b) cancer at smoking associated sites (7–8.5%) and (c) cancer at non-smoking associated sites (33–35%). Only 40% of these cases had no other family member with a neoplastic disease.

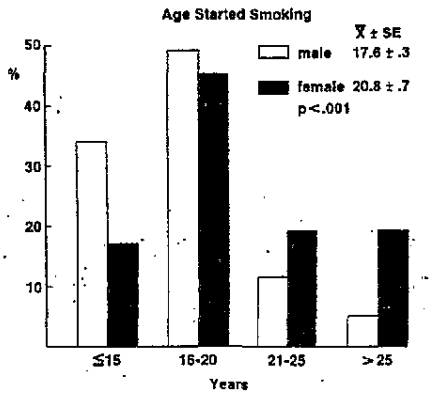

Fig. 3. Distribution and mean age started smoking of individuals with lung cancer stratified by gender.

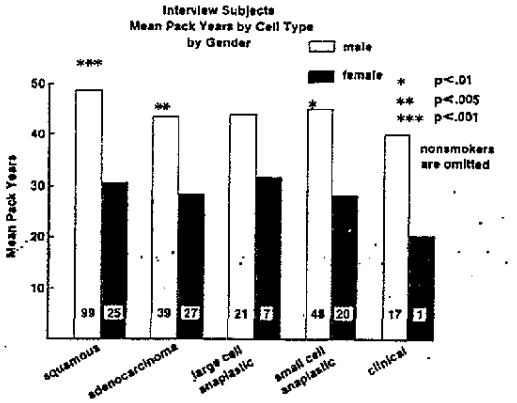

Fig. 5. The mean pack years of individuals with each histological cell type stratified by gender. The number of cases is shown within the bars. Males had significantly higher values then females for squamous cell, adenocarcinoma and small cell anaplastic cell types.

Smoking history

The smoking habits of male and female cases were dissimilar. More (14.6%) lifetime non-smokers among female cases compared with males (3.3%) ($p < 0.001$) (Fig. 2) were found. Females were older when they began smoking (20.8 ± 0.7 vs 17.6 ± 0.3 years, $p < 0.0001$) (Fig. 3). Females smoked fewer cigarettes per day (20.7 ± 0.82 cigarettes vs 26.7 ± 0.8 cigarettes $p < 0.0001$). The female mean pack years, 30.3 ± 1.5, was lower than the male mean pack years, 45.7 ± 1.4 ($p < 0.001$) (Fig. 4).

When the data were stratified by cell type, female mean pack years were significantly lower for squamous cell ($p < 0.001$), adenocarcinoma ($p < 0.005$) and small cell anaplastic ($p < 0.01$) cell types (Fig. 5).

Pulmonary function tests

Only 45 cases, 35 males and 10 females, met the strict criteria for this section of the study, including 2 female non-smokers and 2 male pipe smokers. The remainder were current or ex-smokers of cigarettes. The mean pack years of males ($\bar{X} \pm$ SE, 54.3 ± 4.7) was significantly greater than that of females (30.0 ± 3.5). Minimal differences in the mean percentage of predicted values of the variables FVC, FEV_1, $FEV_1/FVC \times 100$ or MMFR (Fig. 6) were observed.

Occupation and occupational exposures

The most common occupations of males were as follows: farmers (23.1%); farmers with secondary occupations (15.0%); carpenters (5.1%); railroad workers (4.0%); construction and professional drivers (3.3% each); and mechanics (2.9%). Many women were homemakers either non-farm (25.2%) or farm (21.4%). Other frequent occupations were nursing (6.8%), store clerking (5.8%) and office type jobs (4.8%). Of 16 chemicals, groups of chemicals or processes putatively carcinogenic or damaging to the lung,

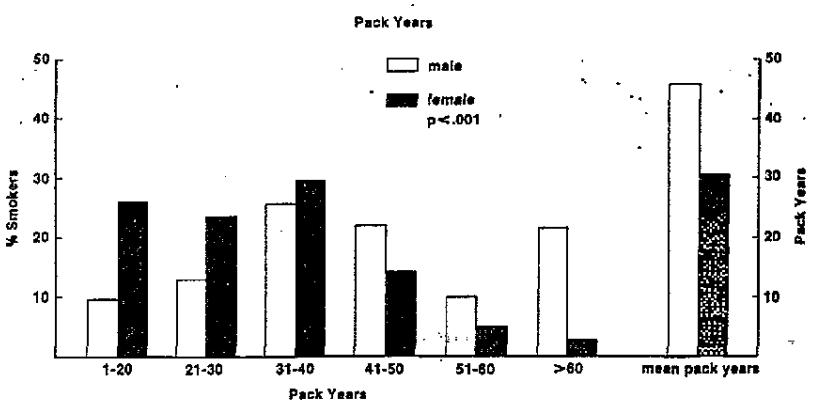

Fig. 4. Distribution and mean pack years of patients with lung cancer stratified by gender.

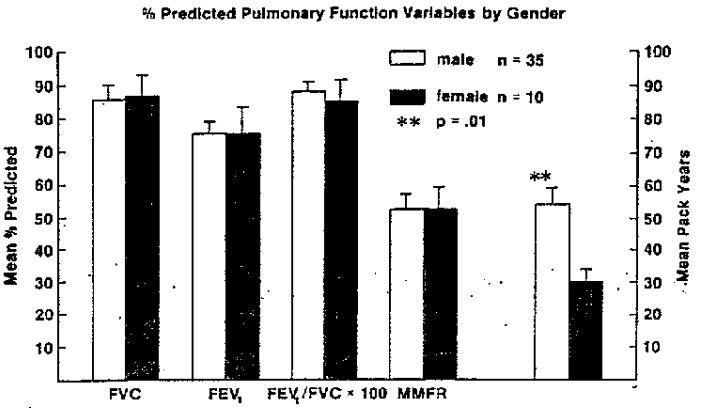

Fig. 6. Mean percentage of predicted pulmonary function variables and mean pack years stratified by gender. The percentage of predicted values adjust for age, gender and height. (FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 sec, MMFR = maximal mid-expiratory flow rate).

a significant proportion of males, i.e. >10%, was exposed to each of 9 of them (Table 2). Only 18% of the men were unexposed to any of the putative occupational carcinogens or deleterious compounds. We compared [36] the occupational exposures of male cases with age-matched male community control subjects and found little correlation between lung cancer risk and occupational exposure to any substance or groups of substances classified by chemical composition. Fewer women reported occupational exposure to each substance.

Survival

Using accumulated survival information on all cases with a diagnosis of primary lung cancer between 1 January 1979 and 31 July 1986 ($n = 2820$), we plotted the survival distribution function vs time in months by sex. In the first months after diagnosis, the curves are virtually identical, after which a consistent survival advantage for women is shown (Fig. 7).

Table 2. Frequency of occupational exposures by sex

	Males		Females	
	n	%	*n*	%
Radiation	16	5.9	2	1.9
Uranium	6	2.2	0	
Grains	172	63.0	30	29.1
Arsenic	29	10.6	8	7.8
Asbestos	35	12.8	2	1.9
Nickel	7	2.6	2	1.9
Chromium	4	1.5	2	1.9
Potash	18	6.6	3	2.9
Diesel fumes	166	60.8	14	13.6
Mining	32	11.7	0	
Welding	91	33.3	0	
Major	11	4.0		
Frequent	12	4.4		
Occasional	68	24.9		
Herbicide	108	39.6	4	3.9
Insecticides	68	24.9		
Fungicides	71	26.0		

DISCUSSION

Histological cell types

Kreyberg [13] classified primary cancers of the lung into those strongly associated with cigarette smoking, squamous cell and small cell carcinomas, and those in which cigarette smoking had a lesser etiologic role, i.e. adenocarcinomas. Several studies have shown sex differences in the distribution of histological cell types [1–3, 5, 9–11]. Squamous cell carcinoma is usually the most prevalent in men and adenocarcinoma in women. In at least two longitudinal studies, the frequency distribution of cell types has been shifting toward more adenocarcinomas in both male and female cases

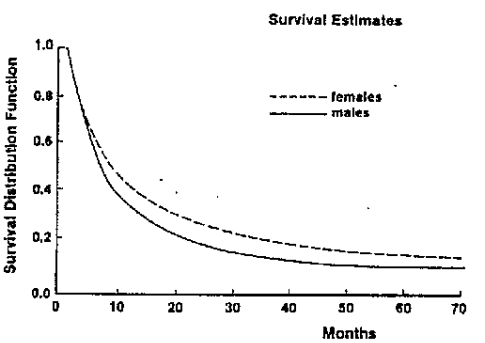

Fig. 7. Survival estimates of all patients with primary lung cancer diagnosed in Saskatchewan between January 1979 and July 1986. The fact that the curves are identical in the first 6 months after diagnosis demonstrates that the younger age at diagnosis of women compared to men is not due to earlier detection of the tumour in women.

[3, 9]. One hospital-based report [14] concluded that there had not been a change in cell type distribution among women. Despite the marked increase in the percentage of female smokers, adenocarcinoma is still the most common cell type among them. In Saskatchewan, using data for all cases diagnosed between 1 November 1983 and 31 July 1986, squamous cell (40%) carcinomas were more than twice as common as adenocarcinomas (16%) or small cell carcinomas (16%) in men. In women, similar frequencies of adenocarcinomas (32%) and squamous cell carcinomas (28%) were reported, while small cell carcinomas were less common (19%). These cell type distributions by sex are not significantly different from the distribution in the interviewed subset. These sex differences in cell type distribution have previously been explained by the sex differences in smoking habits [15]. However, we have recently shown that aside from a higher proportion of lifetime non-smokers among cases with adenocarcinomas, there are non-significant smoking related differences in duration of the habit, mean pack years or distribution of pack years between cases with adenocarcinomas or squamous cell carcinomas stratified by sex [16]. Other investigators used the ever/never smoked dichotomy [2], wherein fewer male cases are lifetime non-smokers compared with female cases. Lubin and Blot [10], in a large European case–control study, showed marked sex differences in cell type distribution among non-smokers, with adenocarcinoma predominating in women.

Antecedent symptoms and medical conditions

Although male cases more frequently reported the chronic symptoms of morning cough and phlegm production, female cases more frequently reported physician diagnosed chronic bronchitis. This discordance may reflect greater utilization of physician services by women. Individuals with chronic bronchitis and/or emphysema are considered to be at higher risk to develop lung cancer [17–20] and a substantial proportion of these cases were affected. Dosman *et al.* [21] conducted a community-based study in the town of Humboldt, Saskatchewan. Although the prevalence of chronic bronchitis was higher in males (20%) than females (9%), the risk of female smokers compared with female non-smokers was 4.4, while that for male smokers compared with male non-smokers was 2.8.

Despite the higher prevalence of physician diagnosed allergies and asthma among women, minimal differences in the prevalence of atopy as measured by allergy skin prick tests were demonstrated. We have demonstrated a lower prevalence of atopy among cases with primary lung cancer compared with age- and sex-matched community controls and with the case's same sex siblings with similar smoking habits [22]. We hypothesized that the mucosal surfaces of the atopic individual more efficiently handle allergens; leading to atopy, and carcinogens; leading to reduced cancer risk although the tumour burden might alter measured reactivity.

Conflicting reports are found in the literature [21, 23–25] concerning sex differences in pulmonary function results as modified by cigarette smoking. Using the percentage of predicted variables of FEV_1, FVC and MMFR, Dosman *et al.* found significantly lower values for female vs male smokers in a community-based study. These sex differences are magnified when expressed as a function of pack years. In our much smaller sample of untreated cases with non-obstructing coin lesions, males and females have similarly depressed pulmonary function values expressed as a percentage of predicted despite an extremely large difference in mean pack years. These data suggest that women may be more susceptible to the effects of cigarette smoking than men. However, in a large longitudinal study, Camilli *et al.* found a steeper decrease in FEV_1/year in male smokers compared with female smokers. The male smokers in that study had significantly greater mean pack years on entry into the study. The largest decline in FEV_1 (40.7 ml/year) was demonstrated in a group of men who smoked more than 40 cigarettes/day.

Familial association

Several investigators [26–29] have reported a familial association of lung cancer with odds ratio between 2.0 and 5.0 in case–control studies. The relationship between personal and familial history of lung disease, specifically chronic obstructive lung diseases and an increased risk of primary lung cancer has also been described [18, 20]. In earlier studies, the familial association was strongest for female relatives, especially non-smokers [26]. We do not confirm this stronger association, the proportion of male and female cases with a confirmed positive family history of

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Survival

The 5-year survival of cases with primary lung cancer has not been improving. Closer monitoring using chest X-rays and sputum cytology, of a high risk group, heavy smoking males over 40 years of age, has not contributed to decreased mortality rates [30]. The unadjusted 5-year survival in our study population is better for women than for men, in agreement with the 1974–1978 data for the province of Alberta [31]. The fact that the curves are identical in the first 6 months suggests that the younger age at diagnosis among women was not a result of earlier detection. In the U.S. SEER data [32], 5-year survival for men has fluctuated from 10 to 12% from 1973 to 1978 and for women from 15 to 18%. Rossing *et al.* [7] demonstrated that women with either squamous cell carcinomas or anaplastic tumours had a better prognosis than men with these cell types. Overall, those cases with anaplastic tumours had a worse prognosis than those with either squamous cell or adenocarcinoma. In a selected group of cases, those eligible for surgery at diagnosis, Kirsh [8] reported that women fared worse than men in 5-year survival and that younger women had the worst prognosis. In their series, those with squamous cell carcinoma had better longer-term survival than those with adenocarcinoma. Hinds *et al.* [33] have demonstrated that lifetime non-smoking women who develop lung cancer have a survival advantage over ex-smokers that persists when adjustment for age at diagnosis, tumour stage, histology and treatment are included.

The increasing prevalence of cigarette smoking among Canadian women, especially young women, has been well-documented [34, 35]. The incidence of primary lung cancer among Canadian women has also risen steeply, despite the fact that women tend to smoke filter and low tar cigarettes in comparison with men [34]. Thus, the introduction of low tar, filter cigarettes and the widespread use of them by women smokers has not been a sufficient response to the dangers of cigarette smoking. We therefore recommend abandonment of this habit and continuing efforts to make cigarette smoking socially unacceptable. Further investigations into the relationship among sex, cigarette smoking habits and deficits in pulmonary function are necessary.

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